

Docket No.: 04712-038002
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
D. Duke LEE et al.

Application No.: 09/153,133

Confirmation No.: 5068

Filed: September 15, 1998

Art Unit: 1627

For: CALCIUM PHOSPHATE DELIVERY
VEHICLE AND ADJUVANT

Examiner: L. Soroush

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicant respectfully requests review of the above-referenced application prior to the filing of an Appeal Brief. Applicant submits the request for review in lieu of a reply to the non-final Office Action dated October 5, 2011. No amendments are being filed with this request and this request is being filed with a Notice of Appeal.

The review is requested for the reasons stated on the attached sheets. If there are any charges or any credits in connection with this request, please apply them to Deposit Account No. 03-2095.

Dated: March 5, 2012

Respectfully submitted,

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REMARKS

The Office rejects claims 45, 46, 58, 59, 73, and 75-77¹ for obviousness over Relyveld (U.S. Patent No. 4,016,252; “Relyveld”) in view of Antonucci et al. (U.S. Patent No. 5,508,342; “Antonucci”) and Gerhart et al. (U.S. Patent No. 5,085,861; “Gerhart”). The Office states, incorrectly, that it would have been obvious to one of ordinary skill in the art at the time of invention to modify the physical characteristics of Relyveld’s composition, based on Gerhart and Antonucci, to form an injectable and hardenable calcium phosphate paste that is “easily administered to a site of interest and [that] readily dissolves in aqueous systems to form stable crystalline structures of HAP” (hydroxyapatite; pp. 3-4 of the Office Action dated October 5, 2011; “the Office Action”). The Office further alleges that a skilled artisan would have been motivated to use an amorphous calcium phosphate (ACP) in the injectable paste because the ordinary artisan would have had a reasonable expectation of success in achieving the same results as Relyveld (Office Action, p. 4). The Office’s conclusion is in error.

Pending independent claim 45 and its dependent claims recite a delivery composition having an ACP or a poorly crystalline apatitic (PCA) calcium phosphate and an antigen or vaccine. The composition is formulated as an injectable paste that hardens in an endothermic reaction at body temperature to form a PCA calcium phosphate. Relyveld, the only cited publication directed to an antigen-containing composition for use in vaccination, only discloses a non-hardenable gel formulation (Abstract) and fails to teach or suggest a paste formulation. Relyveld also fails to teach or suggest an ACP or PCA calcium phosphate composition that hardens to form a PCA calcium phosphate, stating that “the phosphate which constitutes the gel according to the invention has a chemical composition nearer to tricalcium phosphate ($(\text{PO}_4)_2\text{Ca}_3$ ” (col. 2, lines 38-40, and col. 4, lines 4-6). PCA calcium phosphate (also known as “calcium-deficient hydroxyapatite”) of the invention has a structure corresponding to $\text{CA}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}$, which is distinct from the calcium phosphate of Relyveld (see, e.g., Dorozhkin, *Materials* 2:221:291, 2009; Combes et al., *Journal of Biomedical Materials Research, Part A*, 7:318-328, 2006; and ¶ 5 of the Declaration of Michael Strunk, Ph.D. (“the Strunk Declaration”); each of which was previously made of record (see p. 6 of the Reply to Office Action dated

¹ The Office omits reference to the status of pending claim 78 in the Office Action. Since claim 78 was not indicated by the Office as being allowable, Applicant has addressed the present rejections as though they were also applied to pending claim 78.

June 17, 2011 (“the Prior Reply”), which is hereby incorporated by reference)). Finally, Relyveld fails to teach or suggest a calcium phosphate composition that hardens to form a PCA calcium phosphate or that the hardening occurs in an endothermic reaction at body temperature. Thus, Relyveld fails to teach or suggest each and every limitation of pending independent claim 45, and claims dependent therefrom (see *In re Wada and Murphy*, Appeal No 2007-3733 (January 14, 2008) (holding that ‘obviousness requires a suggestion of all limitations in a claim.’)) (citing *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003)).

The Office states that Gerhart and Antonucci provide the limitations absent from Relyveld and that this combination establishes a *prima facie* case of obviousness against pending claims 45, 46, 58, 59, 73, and 75-78. The Office is mistaken, as neither Gerhart nor Antonucci cures the deficiencies of Relyveld noted above.

The Office, at page 3 of the Office Action, cites Antonucci for its disclosure of ACP as the “preferred...mineralizing agent for the formation of HAP” and Gerhart for its disclosure of “biocompatible calcium phosphate ceramics that can be in the form of an injectable or moldable paste and [that] will solidify within 10 minutes after administration.” Like Relyveld, neither Gerhart nor Antonucci teaches or suggests a calcium phosphate composition that hardens to form a PCA calcium phosphate, as is required by pending claims 45, 46, 58, 59, 73, and 75-78. The HAP product of Antonucci is not a PCA calcium phosphate (see, e.g., Table 1 on p. 224, of Dorozhkin, *supra*). And neither are the sintered calcium phosphate ceramics of Gerhart, which, like the calcium phosphate of Relyveld, are “approximately defined by the formula $\text{Ca}_3(\text{PO}_4)_2$ ” (col. 6, lines 59-65, of Gerhart). Thus, even in combination, Relyveld, Gerhart, and Antonucci fail to teach or suggest a calcium phosphate paste composition that hardens to form a PCA calcium phosphate, as is required by pending claims 45, 46, 58, 59, 73, and 75-78.

Further, neither Antonucci nor Gerhart teaches or suggests a calcium phosphate composition that hardens in an *endothermic* reaction at body temperature. Antonucci describes the use of “monomers having acrylate or methacrylate moieties” (see col. 8, lines 66-67) that cure in an *exothermic* reaction to form solid composites (“the unsaturated monomers employed...[and the] polymers which they form...are capable of being quickly and easily cured at *temperatures close to human body temperature*”; col. 8, lines 48-52; emphasis added). The curing of acrylate and methacrylate monomers is known to release heat in an exothermic, not an endothermic,

reaction (the Strunk Declaration, ¶ 8; see also BASF Corporation, “Acrylic Acid: A Summary of Safety and Handling,” 3rd Edition; Atkinson and Grant, *J. Dent. Res.* 44:1040, 1965; Rohm and Hass Technical Bulletin (2006); Knets et al., *J. Achieve. Mater. Manuf. Eng.* 20:135-138, 2006; and Saltzman et al., *J. Orthop. Sports Phys. Ther.* 30:56-67, 2000; each of these publications was previously made of record in the Prior Reply and are incorporated herein by reference).

Similarly, Gerhart describes a composition that hardens in an *exothermic* reaction, stating that the composition includes “particulate biocompatible calcium phosphate ceramics and a resorbable calcium salt dispersed in a cross-linked biodegradable polyester matrix” (see col. 4, lines 22-25), in which “[t]he cross-linking reaction employed to ‘cure’ the present composites is only mildly exothermic compared to, for example, PMMA polymerization” (col. 8, lines 30-32; emphasis added). Nowhere does Gerhart teach or suggest that its compositions can be cured in an *endothermic* reaction at body temperature. Evidence Applicant previously made of record in this application shows that Gerhart’s composition hardens in an *exothermic* reaction having distinctly different energy kinetics when compared to a representative ACP composition prepared according to the methods of the present specification (¶¶ 6 and 7 of the Strunk Declaration).² Thus, no combination of Relyveld, Antonucci, and Gerhart teaches or suggest a calcium phosphate composition that hardens in an *endothermic* reaction at body temperature, as is required by each of the pending claims.

The Office disregards Applicant’s evidence that Gerhart fails to disclose hardening in an endothermic reaction, stating that “Gerhart was not used for the teaching of the paste hardening in an endothermic reaction” (Office Action, p. 25). The Office clearly cites Gerhart for its disclosure of a composition that hardens (“Gerhard [sic] disclose calcium phosphate containing compositions....that...will solidify in 10 minutes”; Office Action, p.3). Yet the Office fails to explain where any of the cited publications discloses a calcium phosphate composition that hardens to form a PCA calcium phosphate in an *endothermic* reaction, as is required to establish a *prima facie* case of obviousness of pending claims 45, 46, 58, 59, 73, and 75-78 (*In re Schreiber*, 128 F.3d 1473, 1478 (Fed. Cir. 1997) (“A patent applicant is free to recite features of an apparatus either structurally or functionally.”); *K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356,

² Applicant also directs the Office to the Declaration of Dr. Aliassghar N. Tofighi (the “Tofighi Declaration”; incorporated herein by reference), which was previously submitted in this application on December 22, 2009. The Tofighi Declaration also addresses

1363 (Fed. Cir. 1999) (“The functional language is, of course, an additional limitation in the [apparatus] claim.”)). The Office, in error, states only that “such [endothermic] hardening will occur because the prior art teaches the same composition as claimed” and “the process of the paste hardening in an endothermic reaction is a property of the [prior art] composition” (Office Action, p. 25). Applicant’s evidence clearly shows this conclusion to be incorrect.

In view of their distinctly different exothermic “curing” reactions, Antonucci and Gerhart, even if combined with Relyveld, would have failed to provide any reasonable expectation of success in the preparation of the endothermically hardening composition of pending claims 45, 46, 58, 59, 73, and 75-78 given the complete absence of any teaching or suggestion in these publications for preparing such a composition. The Office’s conclusions to the contrary are based on factual errors, as none of the cited publications teach or suggest an ACP or PCA calcium phosphate paste that hardens to form a PCA calcium phosphate in an endothermic reaction at body temperature, as is discussed above.

For all the reasons given above, the combination of Relyveld, Antonucci, and Gerhart fails to teach or suggest a composition having each and every limitation of pending claims 45, 46, 58, 59, 73, and 75-78. Further, no combination of Relyveld, Antonucci, and Gerhart would have achieved the composition of pending claims 45, 46, 58, 59, 73, and 75-78 with any reasonable expectation of success. The rejection of claims 45, 46, 58, 59, 73, and 75-78 under 35 U.S.C. § 103(a) for obviousness should be withdrawn.

Obviousness-Type Double Patenting Rejections

The Office rejects claims 45, 46, 58, 59, 73, and 75-78 for nonstatutory obviousness-type double patenting (OTDP) over claims 56 and 57 of U.S. Patent No. 6,541,037. This rejection is moot in view of the Terminal Disclaimer filed on June 17, 2011, in response to this rejection.

Applicant respectfully submits that the remaining OTDP rejections newly raised in this application should be withdrawn because the claims of the cited patents do not appear to be similar to the present claims. Alternatively, these rejections should be held in abeyance until otherwise allowable subject matter is identified.

the exothermic characteristics of the Gerhart composition.